

When rejecting a claim under 35 U.S.C. § 103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993). To establish a *prima facie* case the Examiner must show that the prior art reference, or references when combined, teach or suggest each and every limitation of the claimed invention. M.P.E.P. § 706.02(j). As discussed below, the Examiner has failed to establish that Guo *et al.* and Southern *et al.* teach or suggest each and every limitation of the claimed invention, and thus the Examiner has not established a *prima facie* case of obviousness in this case.

The two independent claims of the instant application, Claims 1 and 6, each comprise four steps: (1) hybridization of overlapping probes to a target nucleic acid; (2) determining the melting temperature of those probes and the target nucleic acid; (3) determining the difference between the melting temperature of the probes and the target and the melting temperature of the probes and a control nucleic acid (the difference is termed " ΔT_m "; (4) determining the difference between the ΔT_m of two overlapping probes (termed the " $\Delta\Delta T_m$ ").

The Examiner states that Southern *et al.* teaches the hybridization of overlapping probes to target sequences, and that mismatched probe/target pairs have significantly lower melting temperatures than matched probe/target pairs. The Examiner then extrapolates from these two teachings that Southern *et al.* also teaches comparing melting temperatures of probes hybridized to target and probes hybridized to controls. The Examiner points to no language in Southern *et al.* to support such an assertion. Finally, the Examiner states that Southern *et al.* also teaches comparing the difference in T_m between probes hybridized to target and probes hybridized control for two overlapping probes. Again, the Examiner does not point to any language in Southern *et al.* to support such an assertion.

The only relevant teaching the Examiner points to is Column 11, Lines 30-34. This passage describes conditions in which a perfectly matched probe/target pair will remain hybridized while probes having mismatches with the target will melt. This disclosure teaches hybridization of matched and unmatched probes with a target, but makes no mention of additionally measuring the melting temperature of probes hybridized to control nucleic acids. While it is true that comparing differences in the melting temperatures of various probes and a

target can reveal the presence of sequence differences in the various probes, such comparisons cannot reveal the location or identity of those sequence differences.

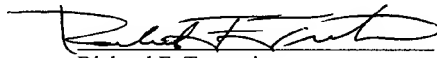
In contrast, the instant invention provides a method whereby the location and/or identity of sequence alterations may be identified. Pinpointing the location and/or identity of the sequence alteration is made possible by comparing the ΔT_m s for two overlapping probes. Comparing the ΔT_m s for two overlapping probes requires two separate hybridizations for each probe, one to a control and one to a target. As discussed above, Southern *et al.* does not disclose such dual hybridizations, rather it discloses comparisons of T_m s for matched and unmatched probes with a target, not ΔT_m s. As neither Guo *et al.* or Southern *et al.* teach or suggest the comparison of ΔT_m for two overlapping probes, the Examiner has not carried her burden in establishing a *prima facie* case of obviousness and the rejection under 35 U.S.C. 103(a) should be withdrawn

CONCLUSION

On the basis of the remarks presented herein, Applicants believe that this application is now in condition for immediate allowance. Applicants respectfully request that the Examiner pass this application to issue, and early notice of such is requested. This paper is filed under 37 C.F.R. section 1.34(a).

Respectfully submitted,
DORSEY & WHITNEY LLP

Date: 4/28/03


Richard F. Trecartin
Reg. No. 31,801

Four Embarcadero Center, Suite 3400
San Francisco, California 94111-4187
Telephone: (415) 781-1989

1109269